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10/577,119	04/13/2007	Gary Kevin Robinson	05794.00004	1176

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EXAMINER	
PORTNER, VIRGINIA ALLEN	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/577,119	ROBINSON ET AL.	
	Examiner	Art Unit	
	GINNY PORTNER	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *13-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-20 are pending; all claims recite a new combination of claim limitations.

Election/Restrictions

1. Applicant's election with traverse of Species 1, down regulation of quorum sensing using a composition comprising a peptide hydrolase in the reply filed on December 11, 2009 is acknowledged. The traversal is on the ground(s) that the reference provided by the examiner to show the lack of unity of invention "appears otherwise unrelated to the present invention " .. because the reference does not use the "peptide hydrolases to hydrolyse LuxR or LuxR homologues involved in quorum sensing". Applicant additonally asserts the reference to "not demonstrate even one occurrence of " the term "LuxR".

2. It is the position of the examiner that none of the claims require the peptide hydrolase to hydrolyze LuxR. The claims recite "modulating"... "by treating the bacteria with a peptide hydrolase". A culture of bacteria must be contacted with the peptide hydrolase, and the biological effects of the peptide hydrolase may be extracellular or intracellular, as long as the hydrolase "modulates the ability of LuxR or a homologue of LuxR to active transcription".

3. US PG-Pub Berka 2003/0027310 clearly teaches the treating of bacteria with a peptide hydrolase

4. [0176] The present invention also relates to methods for preventing biofilm development on a liquid-solid interface by **one or more microorganisms**, comprising **administering an effective amount of a composition comprising one or more polypeptides having** lactonohydrolase **activity** and a carrier to the liquid-solid interface to degrade one or more lactones produced by the one or more microorganisms, wherein the one or more lactones are involved in the formation of the biofilm."

"[0177] The lactone may be any lactone involved in biofilm formation. In a preferred embodiment, the lactone is a homoserine lactone. In a more preferred embodiment, the lactone is

N-(3-oxododecanoyl)-L-homoserine lactone. In another more preferred embodiment, the lactone is N-butyryl-L-homoserine lactone"

5. The lactone is a lactone associated with biofilm formation and examples of LuxR homolgs are provide:

"[0175] The formation of a biofilm by Pseudomonas aeruginosa involves the production of at least two extracellular signals involved in cell-to cell communication (WO 98/58075). The two cell-to-cell signaling systems are the **lasR-lasI and rhlR-rhil** (also called **vsmR-vsml)** systems (Davies et al., 1998, Science 280: 295-298). The lasl gene directs the synthesis of a diffusible extracellular signal, N-(3-oxododecanoyl)-L-homoserine lactone. The lasR product is a transcriptional regulator that requires sufficient levels of N-(3-oxododecanoyl)-L-homoserine lactone to activate a number of virulence genes, including lasi, and the rhlR-rhil system. The rhil gene directs the synthesis of the extracellular signal, N-buytryl-L-homoserine lactone, which is required for activation of virulence genes and expression of the stationary-phase factor, RpoS, by the rhlR gene product. This type of gene regulation has been termed quorum sensing and response. Davies et al have demonstrated that the lasR-lasl system was involved in the differentiation of biofilm formation. WO 98/58075 provides a method whereby cell-cell communication in bacteria via the lasR-lasl system is manipulated to control biofilm architecture and structural integrity. "

Berka discloses three of Applicant's claimed LuxR homologs for modulation, specifically LasR, VsmR and RhlR, and through inactivation of the lactone by treating the bacteria with a lactone peptide hydrolase, the LuxR homolog is not activated, and therefore modulated, the overall activity of the bacteria being down regulated based upon reduced lactone autoinducer

signal being available to the LuxR homolog. Berka does discloses the administration of the lactono-hydrolase to any gram positive or gram negative bacteria [0179].

The examiner is citing James et al (2000) who provide evidence that absent the lactone/LuxR complex forming, translation does not take place (first image) and Shiner et al (2004) shows LuxR to comprise an AIBD:autoinducer binding domain at the N-terminal of the molecule and the C-terminal to comprise a DNA binding domain (HTH), which shows LuxR to be a binding molecule of homoserine lactone molecule, and Berka through inactivation of the autoinducer lactone molecules, modulates down transcripton in the bacteria.

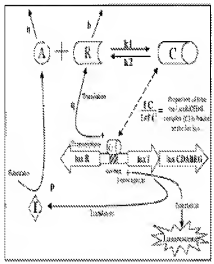

Figure 1. Model for the dynamics between the central components of lux regulation in *Vibrio fischeri*. The binding reaction between OHHL (A) and LuxR (R) to form a complex (C) is described using the rate constants k_1 and k_2 for the binding and dissociation reactions, respectively. The diffusion of A through the cell membrane is determined by the diffusion constant η, and β is broken down according to the constant b. The proportion of time lux box is occupied by complex is described by the expression $[C]/1+[C]$. The rate at which A and R molecules are produced while the complex is bound to the lux box is symbolised by p and q, respectively. The activity of LuxI (I) in synthesising A is included within the constant p, assuming that the availability of substrates is not a limiting factor.

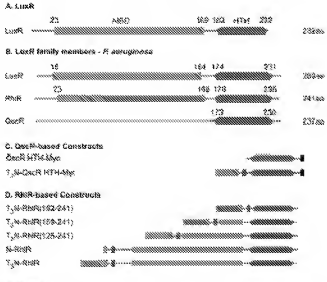

Fig. 1: LuxR-type proteins and constructs used in this study. A. A schematic representation of the domain structure of the founding member of the LuxR family, the **LuxR** protein from *Vibrio fischeri*. The coordinates of the autoinducer binding domain (AIBD, red) and helix turn helix DNA binding domain (HTH, orange) were determined using the Simple Modular Architecture Research Tool (SMART) algorithm (Letunic *et al.*, 2004). **B.** The domain structure of three LuxR-type proteins from *P. aeruginosa* is shown with domain coordinates determined as described above. Note that the SMART algorithm did not detect a consensus AIBD sequence in QscR. **C.** QscR-based chimeric proteins. The structures of chimeric proteins that contain the HTH domain from QscR are shown. Both proteins contain a C-terminal Myc epitope tag (black) and the T7N-QscR HTH-Myc protein contains three copies of the VP16 TAD (green) and the NLS (blue) from the SV40 T antigen (the T7N module) fused to the N-terminus of the HTH domain. **D.** RhlR-based constructs. The coordinates of the segments of RhlR included in the first three constructs are listed at their centre. Each protein contains the T7N module except for N-RhlR, which only contains the N domain. Each protein also includes an N-terminal FLAG epitope tag (purple). **E.** LasR-based constructs. The structure of the single LasR-based protein used in these studies is shown.

6. Therefore Lack of Unity of invention still exists, even in light of Applicant's amendment of the first appearing species of invention. The requirement is still deemed proper and is

therefore made FINAL. Upon further consideration of the species election, and the extensive claim amendments to change the scope of the dependent claims, the examiner will be rejoining species 1 and 2, claims 2-12 for examination. Claims 13-20 stand withdrawn from consideration as being directed to non-elected species of invention

Therefore the claimed inventions are not so linked by a special technical feature that makes a contribution over the prior art. Lack of Unity of invention exists in light of the description and teachings of Berka et al (US PG-Pub 2003/0027310, published February 6, 2003).

Specification

1. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. The hyperlinks located in paragraphs [012], and [031] must be removed.

2. The disclosure is objected to because of the following informalities: at [0023], line 4, appears as the word "Burkhoderia" and should be ---Burkholderia-----. Appropriate correction is required.

Information Disclosure Statement

3. The information disclosure statement filed December 24, 2009 has been considered.

Claim Objections

4. Claims 1-12 are objected to because of the following informalities: Claims 1-12 recite non-elected inventions. Applicant's elected invention is down regulation of LuxR with a peptide

hydrolase, claim 4 recites a plurality of non-peptide hydrolases, specifically chemical compounds, such as CNBr. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. Claim 4 recites the limitation "BNPS skatole," "CNBr", "formic acid", iodosobenzoic acid" and NTCB"" in dependence upon claim 1 which recites "peptide hydrolase". There is insufficient antecedent basis for this limitation in the claim. All of these species are not enzymes and do not meet the description for peptide hydrolase set forth in the instant Specification" "Peptide Hydrolases

[0027] Peptide hydrolases are enzymes that irreversibly hydrolyse amide bonds in peptides and proteins. Peptide hydrolases are widely distributed and are involved in many different biological processes, from activation of proteins and peptides to degradation of proteins."

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

7. Claims 1-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Berka (US PG-Pub 2003/0027310, published February 6, 2003).

Instant claims 1, 6: Berka discloses and claims a method of down regulating quorum sensing in a bacteria,

[0179] The biofilm may be produced by an integrated community of two or more microorganisms or by one microorganism. The microorganism may be any microorganism involved in biofilm production including an aerobic or anaerobic bacterium (**Gram positive and Gram negative**), fungus (yeast or filamentous fungus), algae, and protozoan. In a preferred embodiment, the bacteria is an aerobic bacterium. In another preferred embodiment, the bacterium is an anaerobic bacterium. In a more preferred embodiment, the aerobic bacterium is a **Pseudomonas**. In another more preferred embodiment, the aerobic bacterium is a **Flavobacterium**. In another more preferred embodiment, the anaerobic bacterium is a **Desulfovibrio**. In a most preferred embodiment, the aerobic bacterium is Pseudomonas aeruginosa. In another most preferred embodiment, the anaerobic bacterium is Desulfovibrio desulfuricans.

[0183] The present invention also relates to such compositions for preventing development of a biofilm. Furthermore, the composition may be a disinfectant composition. The disinfectant composition may be useful as a disinfectant for Gram negative bacteria from, including but not limited to, **Pseudomonadaceae, Azatobacteraceae, Rhizabiaeceae, Methylococcaceae, Halobacteriaceae, Legionellaceae, Neisseriaceae.**

Instant claim 1-3: The method of Berka comprising the step of :

Treating the bacteria with a peptide hydrolase

[0176] The present invention also relates to methods for preventing biofilm development on a liquid-solid interface by **one or more microorganisms**, comprising administering an effective amount of a composition comprising one or more polypeptides having **lactonohydrolase** activity and a carrier to the liquid-solid interface to degrade one or more lactones produced by the one or more microorganisms, wherein the one or more lactones are involved in the formation of the biofilm.

[0177] The lactone may be any lactone involved in biofilm formation. In a preferred embodiment, the lactone is a **homoserine** lactone. In a more preferred embodiment, the lactone is N-(3-oxododecanoyl)-L-**homoserine** lactone. In another more preferred embodiment, the lactone is N-butyryl-L-**homoserine** lactone.

to down regulate a LuxR homolog, in gram positive or gram negative bacteria:

[0175] The formation of a biofilm by Pseudomonas aeruginosa involves the production of at least two extracellular signals involved in cell-to cell communication (WO 98/58075). The two cell-to-cell signaling systems are the **lasR-lasI and rhlR-rhil (also called vsmR-vsml)** systems (Davies et al., 1998, Science 280: 295-298). The lasl gene directs the synthesis of a diffusible extracellular signal, N-(3-oxododecanoyl)-L-**homoserine** lactone. **The lasR product is a transcriptional regulator that requires sufficient levels of N-(3-oxododecanoyl)-L-**homoserine **lactone to activate a number of virulence genes,** including lasi, and the rhlR-rhil system. The rhil gene directs the synthesis of the extracellular signal, N-buytryl-L-**homoserine**

lactone, which is required for activation of virulence genes and expression of the stationary-phase factor, RpoS, by the rhlR gene product. This type of gene regulation has been termed quorum sensing and response. Davies et al have demonstrated that the lasR-lasI system was involved in the differentiation of biofilm formation. WO 98/58075 provides a method whereby cell-cell communication in bacteria via the lasR-lasI system is manipulated to control biofilm architecture and structural integrity.

Instant claim 4: wherein the composition comprises a [0182] In a preferred embodiment, the agent is one or more enzymes. In a more preferred embodiment, the one or more enzymes is selected from the group consisting of a protease,…., and describes trypsin-like protease [0084] and aspartic proteinase [0091].

Instant claim 5, 7-8, 9: The method comprising administering the peptide hydrolase to disrupt the quorum sensing being associated with biofilm formation on a solid surface:

Berka claim 34. A method for preventing biofilm development on a liquid-solid interface by one or more microorganisms, comprising administering an effective amount of a composition comprising one or more polypeptides having lactonohydrolase activity and a carrier to the liquid-solid interface to degrade one or more lactones produced by the one or more microorganisms, wherein the one or more lactones are involved in the formation of the biofilm.

As well as… surfaces of medical devises, catheters, orthopedic devices, implants, industrial water processing systems which include materials that are plastic, and metal.

[0172] Thus, the biofilm is a complex assembly of living microorganisms embedded in an organic structure composed of one or more matrix polymers which are secreted by the resident microorganisms.

[0173] Biofilms can develop into macroscopic structures several millimeters or centimeters in thickness and cover large surface areas. These formations can play a role in restricting or entirely blocking flow in plumbing systems, decreasing **heat transfer in heat exchangers**, or causing pathogenic problems in municipal water supplies, food processing, **medical devices (e.g., catheters, orthopedic devices, implants)** and often decrease the life of **materials** through corrosive action mediated by the embedded microorganisms. This biological fouling is a serious economic problem in industrial water process systems, pulp and paper production processes, cooling water systems, injection wells for oil recovery, cooling towers, porous media (sand and soil), marine environments, and air conditioning systems, and any closed water recirculation system.

[0174] The removal or prevention of biofilm traditionally requires the use of dispersants, surfactants, detergents, enzyme formulations, anti-microbials, biocides, boil-out procedures, and/or corrosive chemicals, e.g., base. Procedures for using these measures are well known in the art. For example, removal of biofilm build-up in a paper machine in the pulp and paper industry traditionally requires a deposit control program including proper housekeeping to keep surfaces free of splashed stock, anti-microbial treatment of fresh water and additives, the use of biocides to reduce microbiological growth on the machine, and scheduled boil-outs to remove the deposits that do form.

Instant claims 9,12 wherein the composition is an aqueous, or non-aqueous carrier formulation[0180] The composition comprising one or more polypeptides having lactonohydrolase activity may be a liquid, spray, or powder formulation. A powder carrier is a non-aqueous carrier that is dried.

Instant claim 10: [0180] one or more agents for degrading, removing, or preventing the formation of the biofilm. These agents may include, but are not limited to, dispersants, surfactants, detergents, enzyme formulations, anti-microbials, and biocides. [0181] In a preferred embodiment, the agent is a surfactant. In a more preferred embodiment, the surfactant is sodium dodecyl sulfate, quaternary ammonium compounds, alkyl pyridinium iodides, Tween 80, Tween, 85, Triton X-100, Brij 56, biological surfactants, rhamnolipid, surfactin, visconsin, or sulfonates. [0183] The present invention also relates to such compositions for preventing development of a biofilm. Furthermore, the composition may be a disinfectant composition.

[0187] .... the enzyme may be cell-bound, immobilized on a carrier, or used in a free form using methods well known in the art for enzymatic optical resolution.

Instant claim 11: that may comprise a buffer pH regulator [0199], in combination with

[0199] Chemicals used as **buffers** and substrates were commercial products of at least reagent grade.

Berka et al inherently anticipates the instantly claimed invention as now claimed.

1. Inherently the reference anticipates the now claimed invention. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states AArtisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior arts functioning, does not render the old composition patentably new to the discoverer. The Court further held that Athis same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to GINNY PORTNER whose telephone number is (571)272-0862. The examiner can normally be reached on flextime, but usually M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ginny Portner/
Examiner, Art Unit 1645
February 22, 2010

/Robert B Mondesi/
Supervisory Patent Examiner, Art Unit 1645